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Inherited Disorders of Calcium and Phosphate Metabolism

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Abstract

Purpose of Review—Inherited disorders of calcium and phosphate homeostasis have variable presentation and can cause significant morbidity. Understanding the mode of inheritance and pathophysiology of these conditions will help in the diagnosis and early institution of therapy.

Recent Findings—Identification of genetic mutations in human subjects and animal models has advanced our understanding of many inherited disorders of calcium and phosphate regulation. Identification of mutations of CaSR also has improved our understanding of hypocalcemic and hypercalcemic conditions. Mutations of *Fgf23*, *Klotho* and phosphate transporter genes have been identified as causes for disorders of phosphate metabolism.

Summary—Calcium and phosphate homeostasis is tightly regulated in a narrow range due to their vital role in many biological processes. Inherited disorders of calcium and phosphate metabolism though uncommon can have severe morbidity. Genetic counseling of the affected families is an important part of the follow up of these patients.

Keywords

Hypoparathyroidism; hyperparathyroidism; fibroblast growth factor 23; Klotho

Introduction

Calcium and phosphate play a critical role in many biological functions and are essential components of bone. Regulation of calcium and phosphate homeostasis is tightly controlled with complex interaction between bone, intestine, and kidney. The kidney ultimately regulates serum levels of calcium and phosphate by regulating their transport and urinary losses. Serum calcium and phosphate levels that are routinely measured in clinical practice are not a true reflection of their total body stores as a very small proportion (<1%) of total body stores are present in the serum. While adults are in neutral phosphate and calcium balance, children are in positive calcium and phosphate balance due to growth. There are multiple inherited disorders of calcium and phosphate metabolism resulting in a wide range

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** of outstanding interest

of symptoms which can be challenging to the clinician. In addition, there are nutritional and environmental causes for disturbances of calcium and phosphate homeostasis. For the purpose of this review, we will primarily focus on the inherited disturbances of calcium and phosphate homeostasis, their mode of inheritance, clinical presentation and therapeutic options.

Calcium Homeostasis

Calcium is an essential component of bone and is important for many physiological functions, including muscle contraction, blood clotting, nerve conduction and intracellular signaling. The average adult has 1-1.3 Kg of calcium stores and the vast majority is in the bone (>99%) and about 0.1% is in the extracellular fluid. Unlike adults that are in neutral calcium balance, children are in positive balance as calcium is necessary for bone growth [1]. Calcium is absorbed from the gastrointestinal tract (duodenum and early jejunum) both via nonsaturable paracellular pathway and a 1,25 Vitamin D_3 regulated saturable and active transcellular pathway [2;3]. Serum calcium levels range from 8.5-10.5 mg/dl (.2.1-2.6 mmol/L). Blood calcium exists in three forms; ~45% is protein bound, 45% is free and approximately 10% is complexed to citrate, sulfate, bicarbonate and phosphate. Both complexed and free calcium are filtered across the glomerulus [4]. Of the filtered calcium, about 1% is excreted in urine underscoring the remarkable capacity of the kidney to reabsorb calcium [5]. Serum ionized calcium levels, the physiological active form of calcium, are maintained in a narrow range. Approximately 65-70% of filtered calcium is reabsorbed in the proximal tubule via the paracellular route in an isoosmotic and passive fashion [5-7]. Approximately 20% of filtered calcium is reabsorbed in the thick ascending limb of the Henle across the paracellular pathway; the driving force for this process is the lumen positive potential difference in this segment. Finally, 10-15% of filtered calcium is reabsorbed in the distal convoluted tubule and connecting tubule where calcium reabsorption is active, transcellular and tightly regulated. The transient receptor potential vanilloid 5 (TRPV5) channel is primarily responsible for calcium uptake in the distal tubular cells, intracellular calcium is bound to calbindin-D28K and is transported to the basolateral membrane where calcium exits to the intravascular space by two transporters; sodium/calcium exchanger 1 (NCX1) and plasma membrane calcium ATPase isoform 1b (PMCA1b) [8].

Regulation of calcium homeostasis involves two important hormones; parathyroid hormone (PTH) and 1,25 Vitamin D_3. The parathyroid gland senses serum ionized calcium levels through calcium sensing receptor (CaSR) and regulates PTH synthesis and secretion [9]. Low ionized calcium inactivates CaSR and stimulates PTH secretion while high calcium levels activate the receptor which results in decreased PTH secretion. PTH regulates calcium homeostasis via activating the PTH receptor which increases active reabsorption of calcium in the kidney. PTH activates osteoclastic bone resorption through the RANKL (receptor activated of nuclear factor κB ligand), osteoprotegerin and RANK system [10]. PTH stimulates 1 α hydroxylase in the proximal tubule, the enzyme responsible for conversion of 25 Vitamin D to 1,25 Vitamin D_3, which increases calcium absorption from the gastrointestinal tract and kidney by increasing the expression of transcellular calcium transport machinery [11;12]. 1,25 Vitamin D_3 also stimulates bone resorption. Dietary calcium also plays an important role in regulating calcium homeostasis as seen in mice with the absence of either the vitamin D receptor or 1α-hydroxylase. In these mice an increase in calcium intake increases calcium absorption in both the intestine and kidney which increases serum calcium levels [11-13].

Hypocalcemia

Hypocalcemia can affect many organ systems and causes arrhythmias, prolongation of QTc interval, hypotension, coarse hair, dry skin, muscle twitching and tingling, paresthesias, tetany, and seizures. Trousseau's and Chvostek's signs are used to examine for increased neuromuscular activity. Chvostek sign is noted by contraction of facial muscles by tapping on the facial nerve near the temporomandibular joint and Trousseau's sign is elicited by inflating the blood pressure (BP) cuff above the patient's systolic BP for 3 minutes which results in spasm of the involved hand. The inherited causes of hypocalcemia can be broadly classified in to disorders of vitamin D metabolism, CaSR and parathyroid gland. These conditions are outlined in table 1 [14;15].

Hypoparathyroidism

Familial isolated hypoparathyroidism can be inherited in an autosomal recessive, dominant or X-linked fashion and the mutations are noted either in the genes regulating parathyroid gland development or the PTH gene itself. Patients usually present in the neonatal period with seizures, hypocalcemia, hyperphosphatemia, low 1,25 Vitamin D_3 and low or inappropriately normal PTH levels. Therapy includes calcium and 1,25 Vitamin D_3 supplements. Hypoparathyroidism can be part of the DiGeorge syndrome which is a constellation of malformations including hypoplasia of pharyngeal arches, thymus absence/ hypoplasia, cardiac and craniofacial defects due to deletion of 22q11.2 in most patients. Hypocalcemia is usually noted in 50-60% of the neonates and can be transient but hypocalcemia can also present for the first time in adulthood [16;17].

Autosomal Dominant Hypercalciuric Hypocalcemia

Autosomal dominant hypercalciuric hypocalcemia (ADHH) or familial benign hypercalciuric hypocalcemia (FBHH) is due to gain of function mutation of CaSR resulting in a higher serum calcium threshold necessary for PTH secretion. Patients have mild hypocalcemia, inappropriately normal or low PTH levels, hypomagnesemia and hypercalciuria and are usually asymptomatic. If asymptomatic patients are treated with calcium and 1,25 Vitamin D_3 supplements, the hypercalciuria can worsen and result in nephrocalcinosis. The aim is not to normalize calcium but is to keep the patients asymptomatic with minimal dose of supplements [18;19].

Pseudohypoparathyroidism

Pseudohypoparathyroidism type 1a (PHP-Ia), known as Albright's hereditary osteodystrophy is characterized by hypocalcemia, hyperphosphatemia and elevated PTH levels due to resistance to PTH. It is inherited in an autosomal dominant fashion and results from mutations in the *GNAS1* gene which encodes for $G_s\alpha$ subunit. $G_s\alpha$ is a subunit of G_s protein which stimulates cyclic AMP production by several hormones including PTH, thyrotropin, and gonadotropin releasing hormone [20;21]. Clinical features include obesity, short stature, brachydactyly, ectopic calcifications, developmental delay and multiple endocrine deficiencies. Pseudopseudohypoparathyroidism (pPHP) is also an autosomal dominant condition that has similar physical presentation as PHP-Ia but lacks other endocrine deficiencies. Patients with both PHP-Ia and pPHP can be found in the same extended family due to parental imprinting of hormone resistance. Patients with PHP-Ia have inherited the mutated gene from their affected mother with either PHP-Ia or pPHP and patients with pPHP have inherited the mutation from their father [22;23]. Pseudohypoparathyroidism type Ib is characterized by PTH resistance and is caused by loss of methylation with in GNAS1 on the maternal allele. The clinical features include hypocalcemia, hyperphosphatemia and some of these patients have also shown resistance to thyrotropin and have shortened 4^{th} metacarpal [24;25]. Therapy involves calcium and 1,25 Vitamin D_3 supplements while monitoring for hypercalciuria and nephrocalcinosis.

Vitamin D- Dependent (Resistant) Rickets

Vitamin D is either produced in the skin or is ingested in the diet. Vitamin D is hydroxylated in the liver by 25 hydroxylase to 25 Vitamin D, the most abundant circulatory form of vitamin D. It is further hydroxylated by 1 α hydroxylase to 1,25 Vitamin D_3, the active form of Vitamin D and 1 α hydroxylase is tightly regulated by PTH, fibroblast growth factor 23 (FGF23), calcium, phosphate and by 1,25 Vitamin D_3 itself. Vitamin D dependent rickets type 1 (Pseudovitamin D-deficiency rickets) is due to mutations in the 1 α hydroxylase gene resulting in either absence or decreased function of 1 α hydroxylase activity and is inherited in an autosomal recessive fashion. Patients usually present at few months after birth to 2 years of age with seizures, hypotonia growth delay, signs of rickets (prominent forehead, rachitic rosary, enlarged wrists and ankles). Evaluation reveals hypocalcemia, hypophosphatemia, elevated levels of PTH and alkaline phosphatase, very low 1,25 Vitamin D_3 levels. 25 vitamin D levels are usually normal in these patients. Treatment is with 1,25 Vitamin D_3 supplementation [26;27].

Vitamin D-dependent rickets type 2 (Vitamin D resistant rickets) is due to mutation in the vitamin D receptor (VDR) and is inherited in an autosomal recessive manner with heterogeneous presentation. Patients usually present within months after birth with rickets. Biochemical abnormalities are similar to Vitamin D dependent rickets type 1 except that 1,25 Vitamin D_3 levels are elevated. Another unique feature that is seen in these patients is alopecia totalis. Treatment in these patient can be challenging, however, some patients do respond to high doses of 1,25 Vitamin D_3 or its analogues. Patients who do not respond can be treated with oral and IV calcium salts with limited success [28;29].

Hypercalcemia

The symptoms of hypercalcemia are dependent not only on the severity of hypercalcemia but the rate of rise in serum calcium levels. The spectrum of symptoms includes three mains organ systems; renal, GI, neurological and cardiac. Patients can present with constipation, loss of appetite, weight loss, abdominal pain, acute pancreatitis, vomiting, irritability, poor concentrating capacity, memory loss, muscle weakness, lethargy, hypertension, shortened QTc interval and cardiac arrhythmias. Renal symptoms include polyuria, polydipsia, volume depletion, nephrocalcinosis and renal failure. The inherited disorders of hypercalcemia can be broadly classified in to disorders of parathyroid gland, CaSR and PTH receptor and are shown in table 1 [15;30].

Hyperparathyroidism

Parathyroid tumors are rare in children and when they occur they are usually part of inherited tumor syndromes. Multiple endocrine neoplasia type 1 (MEN1) is an autosomal dominant disorder caused by mutation in the tumor suppressor gene (*MEN 1*). Patients can have parathyroid, pancreatic or anterior pituitary tumors. Patients with MEN type 2 have activating mutations in the *RET* proto-oncogene and is inherited in an autosomal dominant fashion. Parathyroid tumors in MEN type 2 occur late in adulthood and patients have medullary carcinoma of the thyroid and pheochromocytoma. Patients with hyperparathyroidism present with hypercalcemia, hypophosphatemia, increased urinary calcium, decreased fractional excretion of phosphate (FePhos) and elevated PTH levels [31;32].

Familial Hypocalciuric hypercalcemia/Neonatal severe primary hyperparathyroidism

Familial hypocalciuric hypercalcemia (FHH) is characterized by mild hypercalcemia, inappropriately normal or mildly elevated PTH levels and hypocalciuria. In most patients FHH is due to inactivating mutations of the CaSR and is inherited in an autosomal dominant manner. CaSR on the parathyroid gland is insensitive to the elevated serum calcium levels and there is a “right shift” set point for PTH release, the opposite of what is seen in autosomal dominant hypercalciuric hypocalcemia. Mutated CaSR in the kidney results in hypocalciuria and this distinguishes patients from primary hyperparathyroidism where there is increased urinary calcium. Most of the patients with FHH are asymptomatic and thus do not warrant treatment. Parathyroidectomy is contraindicated in these patients and treatment options for symptomatic patients include thiazide diuretics and calcimimetics [33;34].

Neonatal severe primary hyperparathyroidism (NSHPT) is usually inherited in an autosomal recessive manner and patients have homozygous inactivating mutations of the CaSR. Clinical features include severe hypercalcemia, elevated PTH levels, hypophosphatemia, failure to thrive, polyuria, hypotonia, and bone deformities. Treatment options include aggressive IV hydration, bisphosphonates, calcimimetics and reserving subtotal parathyroidectomy for severe cases resistant to medical therapy [33;34].

Idiopathic Hypercalcemia of Infancy (Lightwood syndrome)

Hypercalcemia is noted in these patients between 6-12 months of age. Other features of Lightwood syndrome are failure to thrive, vomiting, dehydration, hypercalciuria and nephrocalcinosis. Patients usually do not exhibit any dysmorphic features and lack cardiac anomalies. PTH levels are commonly suppressed with upper limits of normal to elevated 25 Vitamin D_3 and 1,25 Vitamin D_3. Recently, mutations of 24 hydroxylase gene have been noted in these patients and the inheritance appears to be autosomal recessive. This mutation therefore will predispose children to develop hypercalcemia when supplemented with vitamin D. Even though Lightwood syndrome is rare, it is important for physicians to be aware of this condition due to the increasing use of vitamin D supplementation in healthy children and adults [35-37].

Jansen's Metaphyseal Chondrodysplasia

Jansen's Metaphyseal Chondrodysplasia is due to constitutive activation of the PTH receptor resulting in hypercalcemia, hypophosphatemia and abnormal chondrocyte proliferation and is inherited in an autosomal dominant manner. Patients have short stature with short extremities with normal PTH and PTH related peptide levels [38].

Phosphate Homeostasis

Phosphate plays a vital role in many physiological functions including cell structure, energy metabolism, oxygen transport, intracellular signaling, and as urinary and serum buffer. Phosphate is an important component of the skeletal system. An average adult has ~700 gm of phosphate and the majority of which (85%) is in the skeleton with ~1% in the extracellular fluid. Inorganic free phosphorus (phosphate) is measured by the laboratories and normal values are in the range of 3-4.5 mg/dl (1-1.5 mmol/L). Small portion of serum phosphate ~10% is protein bound. Neonates are in positive phosphate balance due to their increased needs for skeletal development. Phosphate is absorbed from GI tract via a paracellular, non-saturable process and an active transcellular pathway via the sodium phosphate cotransporter 2b (NaPi2b). NaPi2b is regulated by dietary phosphate, metabolic acidosis and 1,25 Vitamin D_3. After phosphate reaches the circulation, free and complexed phosphate is filtered and ~80-90% is reabsorbed by the kidney primarily via two transporters on the apical membrane of the proximal tubule designated NaPi2a and NaPi2c. Phosphate homeostasis is primarily regulated by dietary phosphate, 1,25 Vitamin D_3, PTH, fibroblast growth 23 (FGF23) and Klotho

PTH though primarily a calcium regulatory hormone inhibits renal phosphate reabsorption causing urinary phosphate wasting by decreasing the expression of NaPi2a and NaPi2c. PTH increases the synthesis of 1,25 Vitamin D_3 in the proximal tubule which in turn increases GI absorption of phosphate via NaPi2b. Low dietary phosphate decreases and high dietary phosphate increases renal phosphate excretion. FGF23 increases renal phosphate wasting by inhibiting NaPi2a and NaPi2c in the proximal tubule. Additionally, FGF23 decreases expression 1 α hydroxylase and increases expression of 24 hydroxylase with the net result of lower 1,25 Vitamin D_3 levels [39;40]. Klotho is an essential coreceptor for FGF23 but Klotho independently has been shown to cause renal phosphate wasting [41].

Hypophosphatemia

The acute symptoms of hypophosphatemia include myopathy, fatigue, bone pain, increased risk for rhabdomyolysis and hemolysis. Respiratory and cardiac failure can occur with hypophosphatemia. Chronic hypophosphatemia results in skeletal abnormalities including rickets and osteomalacia. Inherited hypophosphatemic conditions can be classified in to FGF23 dependent and FGF23 independent disorders and are outlined in table 1.

Syndromes of FGF23 Excess

Autosomal dominant hypophosphatemic rickets (ADHR) is characterized by phosphaturia, hypophosphatemia and inappropriately normal or low 1,25 Vitamin D_3. Patients also can have dental dysplasia and enthesopathies (painful mineral deposits at the site of tendon insertion). Serum calcium and PTH levels are usually normal. ADHR is due to mutation of the FGF23 protein at the arginine residues either at 176 or 179 position ($R^{176}XXR^{179}$) making it resistance to cleavage by proteases. FGF23 levels are thus elevated in these patients. ADHR has a variable penetrance even within the same family. ADHR has dichotomous presentation: adolescence/adulthood (group 1) or childhood (group 2). Group 1 presents with muscle weakness, bone pain, and fractures but with no bone deformities while group 2 presents with rickets and bone deformities. In many of the group 1 patient's pregnancy was a precipitating factor for their presentation. In some patients with childhood presentation, renal phosphate wasting resolves after puberty [42].Treatment options include phosphate supplements and calcitriol.

X linked hypophosphatemic rickets (XLH) is the most common (1:20,000) inherited form of rickets and is inherited in an X linked recessive manner. XLH is due to mutation in the *PHEX* (Phosphate regulating gene with Homologies to Endopeptidases on the X-chromosome) gene. It is unclear as to how mutations of the *PHEX* gene result in elevated serum FGF23 levels. Males and females are affected and their clinical presentation is similar to patients with ADHR. Additional features include short stature, frontal bossing and craniosynostosis. Treatment options include phosphate supplements and calcitriol which improves symptoms but does not normalize serum phosphate levels [43-45]. Treatment complications include hypercalciuria, nephrocalcinosis and secondary hyperparathyroidism. Cinacalcet can be used to treat secondary hyperparathyroidism [46]. Future treatment options include FGF23 neutralizing antibodies which have shown improvement in hypophosphatemia and rickets when used in a mouse model of XLH (*Hyp* mouse) [47;48].

Autosomal recessive hypophosphatemic rickets (ARHR) is a rare disease which is due to inactivating homozygous mutations of dentin matrix protein 1 (DMP1) or ecto-nucleotide pyrophosphatase/phosphodiesterase 1 (ENPP1) genes. Patients with ARHR have inappropriately normal or elevated levels of FGF23 and it is yet unknown how DMP1/ENPP1 mutations cause elevated FGF23 levels. Clinical presentation and treatment options are similar to ADHR and XLH [49-51].

Fibrous dysplasia is characterized by fibrous skeletal lesions which exist in two forms: monostotic and polyostotic. McCune Albright syndrome is due to activating mutations of GNAS-1 which encodes for $G_s\alpha$ subunit and is characterized by Café-au-lait spots, precocious puberty and polyostotic fibrous dysplasia. Some of these fibrous dysplasia lesions can secrete FGF23 which causes a phenotype similar to XLH, ARHR and ADHR. It is unknown as to why these fibrous lesions produce FGF23 when GNAS-1 is mutated. Treatment is symptomatic with phosphate supplements, calcitriol and recently bisphosphonates has been used with some success [52;53].

Translocation of the *Klotho* gene resulting increased Klotho levels has been described in one patient causing hypophosphatemia, hyperparathyroidism needing parathyroidectomy, hypercalcemia, and inappropriately normal 1,25 Vitamin D_3 levels. [54].

FGF23 Independent Hypophosphatemic disorders

Hereditary hypophosphatemic rickets with hypercalciuria (HHRH) is an autosomal recessive disease and is due to mutations of *NaPi2c*. Patients present with bone pain, weakness, fractures, short stature and rickets. Patients have hypophosphatemia, phosphaturia, hypercalciuria, elevated 1,25 Vitamin D_3 and low PTH levels. Hypophosphatemia is potent stimulus for 1α hydroxylase which increases serum 1,25 Vitamin D_3 levels which in turn increases GI absorption of calcium and phosphate and decreases PTH levels. In the face of suppressed PTH levels, patients develop hypercalciuria with the risk of developing nephrocalcinosis and decreased bone mineral density. Treatment is primarily with phosphate supplements. Treatment with calcitriol will worsen hypercalciuria and should not be used [55;56]. *NaPi2a* mutations unlike *NaPi2c* develop autosomal recessive Fanconi syndrome. The reason for the difference in presentation when the different proximal tubule phosphate transporters are mutated is not clear[57].

Inherited forms of primary hyperparathyroidism, activating mutations of PTH receptor, Vitamin D dependent rickets types 1 and 2 can also present with hypophosphatemia and are described in the hypocalcemia section.

Hyperphosphatemia

The acute symptoms of hyperphosphatemia are primarily due to the resulting hypocalcemia and its symptoms [58]. An acute phosphate load especially after phosphate enemas has been shown to cause phosphate nephropathy and acute kidney injury [59]. Chronic hyperphosphatemia has been associated with vascular calcifications especially in patients with chronic kidney disease and end stage renal disease [60]. Inherited hyperphosphatemic conditions can be classified in to FGF23 dependent and FGF23 independent disorders. These are outlined in Table 1.

FGF23 deficiency disorders

Familial tumoral calcinosis is primarily inherited as an autosomal recessive disorder with hyperphosphatemia, hypercalcemia, elevated or inappropriately normal levels of 1,25 Vitamin D_3 and ectopic calcifications which can be painful. Serum calcium and PTH levels are usually normal. Two mutations have been identified: *GALNT3* and *FGF23* genes. GALNT3 encodes for a glycosyltransferase which glycosylates threonine^{178}, at the cleavage site, $R^{176}XXR^{179}$ of FGF23. The resultant mutant FGF23 protein is prone to increased degradation by proteases. Inactivating mutations of the *FGF23* gene results in mutant FGF23 which is either not secreted in its intact form or is cleaved faster by proteases. In both of the mutations, the intact FGF23 levels are low while C-terminal FGF23 levels are elevated [61;62].

Tumoral calcinosis with the phenotype as described above was seen in a 13 year old patient who was found to have a homozygous missense mutation of the *Klotho* gene. However, patient was noted to have elevated both intact and C-terminal FGF23 levels. In vitro studies demonstrated that the mutant Klotho protein was less stable and had lower expression [63]. As Klotho is an essential coreceptor for FGF23, mutation of the Klotho protein causes resistance to FGF23 and thus resulting in a phenotype similar to FGF23 deficiency.

Inherited causes of hypoparathyroidism and pseudohypoparathyroidism are described in the hypocalcemia section.

Conclusion

Inherited disorders of calcium and phosphate homeostasis have variable presentation. The primary organs involved in calcium and phosphate metabolism are the kidney, bone, parathyroid gland and the GI tract. The hormones involved are PTH, FGF23, Klotho and 1,25 Vitamin D_3. Careful step wise evaluation of these organ systems and hormones will greatly aid in the diagnosis process. Identifying the exact defect will in these disorders will guide treatment options. Importantly, genetic counseling should be provided to the affected families.

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Keywords

- Calcium and phosphate homeostasis if tightly regulated due to their vital role in many biological processes.
- Inherited disorders of calcium metabolism are primarily due to abnormalities of PTH and its receptors, Vitamin D metabolism and CaSR.
- Inherited disorders of phosphate metabolism are primarily due to abnormalities of FGF23, PTH, sodium phosphate transporters and Klotho.

Table 1

Inherited Disorders of Calcium and Phosphate Homeostasis

Hypocalcemic conditions		
Disease	**Genetic Mutation**	**Pathogenesis of the disease**
Familial hypoparathyroidism	GCMB SOX3	Altered parathyroid gland development
DiGeorge syndrome	22q.11 deletion	Hypoplasia of pharyngeal arches
Autosomal dominant hypercalciuric hypocalcemia	CaSR	Gain of function of CaSR
Pseudohypoparathyroidism	GNAS1	Defective Gsαsubunit
Vitamin D dependent rickets Type 1	1α hydroxylase	Low/undetectable 1,25 Vitamin D_3 levels
Vitamin D dependent rickets Type 2	Vitamin D receptor	Resistance to the effects of 1,25 Vitamin D_3
Hypercalcemic conditions		
Disease	**Genetic Mutation**	**Pathogenesis of the disease**
Hyperparathyroidism	*MEN1* MEN2 *(RET)*	Inherited tumor syndromes
Familial hypocalciuric hypercalcemia	CaSR	Inactivating mutation of CaSR
Hypophosphatemic Conditions		
Disease	**Genetic Mutation**	**Pathogenesis of the disease**
X-linked hypophosphatemic rickets	*PHEX*	Increased boneFGF23 protein expression
Autosomal dominant hypophosphatemic rickets	*FGF23*	Mutant FGF23 protein is resistant to degradation
Autosomal recessive hypophosphatemic rickets	*DMP1* *ENPP1*	Increased bone FGF23 protein expression
Hereditary hypophosphatemic rickets with hypercalciuria	*NaPi2c*	Loss of proximal tubular NaPi2c function
Autosomal recessive Fanconi syndrome, hypophosphatemic rickets	*NaPi2a*	Loss of proximal tubular NaPi2a function
Hypophosphatemic rickets	*Klotho*	Overexpression of Klotho results in hypophosphatemia
Hyperphosphatemic conditions		
Disease	**Genetic Mutation**	**Pathogenesis of the disease**
Tumoral Calcinosis	*FGF23* *GALNT3* *Klotho*	Decreased production or increased degradation of FGF23. Resistance to FGF23 due the absence of Klotho

GCMB- glial cells missing B, SOX3 - Sry-related HMG box

Adapted from [14]